REMARKS

I. INTRODUCTION

Applicants thank the Examiner for the indication that claims 26, 70 and 71 include allowable subject matter.

Claims 5 and 6 have been cancelled above, without prejudice. Claims 1 and 39 have been amended above to include the subject matter recited in now-cancelled claims 5 and 6. Claims 11, 26, 70 and 71 have been rewritten in independent form. New claims 82 and 83 are added. Accordingly, claims 1-4, 7-27, 39-43, 62-69 and 72-83 are now under consideration in the above-referenced application. Provided above, please find a claim listing indicating the current amendment to the previously-pending claims on separate sheets so as to comply with the requirements set forth in 37 C.F.R. § 1.121. It is respectfully submitted that no new matter has been added.

II. REJECTIONS UNDER 35 U.S.C. §§ 102 AND 103(a) SHOULD BE WITHDRAWN

Claims 1-3, 10, 12, 14-20 and 39 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Zimnyakov et al., "Spatial speckle correlometry in applications to issue structure monitoring," Applied Optics, Col. 36, No. 22, August 1, 1997, pp. 5594-5607 (the "Zimnyakov publication"). Claims 1-10, 12, 12, 21, 22, 24, 25, 39 and 75 stand rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent Application Publication No. 2002/0016533 A1 by Manchitto et al. (the "Manchitto Application"). Claim 11 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over the Manchitto Application or the Zimnyakov publication. Claim 23 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over the Manchitto Application. Claim 13 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over the Manchitto Application, in

view of M. Facchini et al., "An endoscopic system for DSPI," Optik International Journal for Light and Electron Optics, Vol. 95, November 1993, pp. 27-30 (the "Facchini publication"). Claims 14-20, 27 and 72 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over the Manchitto Application, in view of U.S. Patent No. 5,065,331 issued to Vachon et al. (the "Vachon Patent"). Claims 40, 62-64, 68, 73, 74, 77, 79 and 81 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over the Manchitto Application, in view the Vachon Patent, and in further view of U.S. Patent No. 6,816,743 issued to Moreno et al. (the "Moreno Patent"). Claims 41-43 and 65-67 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over the Manchitto Application, in view the Vachon Patent and the Moreno Patent, and in further view of D.A. Boas et al., "Diffusing temporal light correlation for burn diagnosis," SPIE, Vol. 2979, 1997, pp. 468-477 (the "Boas publication"). Claims 69, 78 and 80 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over the Manchitto Application, in view the Vachon Patent and the Moreno Patent, and in further view of Howard M. Loree et al., "Mechanical Properties of Model Atherosclerotic Lesion Lipid Pools," Arteriosclerosis and Thrombosis, Vol. 14(2), 1994, pp. 240-247. (the "Loree publication").

Applicants respectfully request the 35 U.S.C. §§ 102 and 103(a) rejections be withdrawn for at least the reasons set forth herein below.

A. Rejections of Claims based on the Manchitto Application

Pursuant to 37 C.F.R. § 1.131 and M.P.E.P. § 715(I)(B), Applicants hereby antedate the Manchitto Application, and thus respectfully assert that this reference is not an effective reference for rejecting amended independent claims 1 and 39 of the above-identified application (and the claims which depend there from) under 35 U.S.C. § 102(e). In particular, Applicants

submit herewith a Declaration under 37 C.F.R. § 1.131 (the "Rule 131 Declaration") and supporting documents therefor. In this Rule 131 Declaration, the inventors – Dr. Tearney and Dr. Bouma – confirm that that they conceived the invention recited in amended independent claims 1 and 39 on or before May 3, 2000, which is the effective 35 U.S.C. § 102(e) date of the Manchitto Application with respect to the claims of the present application.

Accordingly, the rejection of claims 1-10, 12, 12, 21, 22, 24, 25, 39 and 75 under 35 U.S.C. § 102(e) as being anticipated by the Manchitto Application is now moot. In addition, because the Manchitto Application is no longer an effective 35 U.S.C. § 102(e) reference for rejecting the claims of the application, this publication cannot be combined with any of the Facchini publication, the Vachon Patent, the Moreno Patent, the Boas publication, and/or the Loree publication to render any of the claims referenced herein above obvious under 35 U.S.C. § 103(a). Accordingly, the § 103 rejections of claims 13-25, 27, 40, 62-69, 72-74 and 77-81 are also moot for the same reasons, and because such references (without combining them with the Manchitto Application) in no way teach or suggest the subject matter recited in these claims.

Therefore, at least because the Manchitto Application has been antedated with respect to the above-reference claims of the present application, Applicants respectfully assert that the §§ 102(e) and 103(a) rejections of these claims as being anticipated by the Manchitto Application or rendered obvious by this publication in combination with other references are now moot. Accordingly, these §§ 102(e) and 103(a) rejections should be withdrawn.

B. Rejections of Claim 11 based on Manchitto Application/Zimnyakov Publication

Applicants' invention, as recited in independent claim 11 (which has been rewritten in independent form), relates to a method of analyzing tissue, which comprises the steps of, *inter alia*:

> illuminating a tissue with coherent or partially coherent light;
>
> receiving light reflected from the tissue at a detector and forming series of speckle patterns; and
>
> analyzing changes in the speckle patterns at time intervals sufficient to measure changes caused by microscopic motion of objects within the tissue, **wherein the partially coherent light comprises light from a superluminescent diode**.

The Examiner admits that the Manchitto Application and the Zimnyakov publication fail to address the use of a superluminescent diode. (See Office Action dated March 8, 2005, p. 4, lns. 13 and 14). However, the Examiner contends that "it would have been an obvious matter of design choice to a person of ordinary skill in the art to use a superluminescent diode, because Applicant has not disclosed that such a light source provides an advantage, is used for a particular purpose, or solves a stated problem." (*Id.*, p. 4, lns. 14-16). Applicants respectfully disagree.

In particular, the Manchitto Application only describes the use of an illuminating light which consists of alternating pulses of radiant energy produced by light-emitting diodes (LEDs) filtered with a bandpass filter, or diode lasers to produce radiant energy impinging on the surface. (See Manchitto Application, paragraph [0030]). The Zimnyakov publication only describes the use of a single mode He-Ne laser with a 2-mW generating a linearly polarized Gaussian beam that is expanded by the telescopic system. (See Zimnyakov publication, p. 5595, 2nd column, last full paragraph). However, as the Examiner admitted, the Manchitto Application and the Zimnyakov

publication provide absolutely no disclosure, teaching or even a suggestion to substitute Manchitto Application's LEDs or diode lasers or Zimnyakov publication's He-Ne laser with *the superluminescent diode*, as recited in independent claim 11. Simply stated, the Manchitto Application and the Zimnyakov publication nowhere mention that any light source, other than their described LEDs or lasers can be used with its system to obtain the desired results.

The Examiner further contends that "[o]ne of ordinary skill in the art, furthermore, would have expected Applicant's invention to perform equally well with the coherent light sources of the Manchitto et al. or Zimnyakov et al. [to] detect speckle changes caused by microscopic motion of objects in tissue." (Office Action, p. 4, lns 18-21). However, it is improper to utilize Applicants' disclosure as a "roadmap" for selecting and inserting various aspects of the claimed invention – such knowledge must come from the prior art, without the use of Applicants' disclosure. In particular, it appears that the Examiner is attempting to locate the teachings that are missing from the Manchitto Application or the Zimnyakov publication, without providing the adequate motivation or incentive to do so. By such "picking and choosing" missing elements, the Examiner is believed to be employing an improper hindsight reconstruction. "It is improper to use the inventor's disclosure as a road map for selecting and combining prior art disclosures." *Grain Processing Corp.* 840 F.2d at 907. "[T]he reference must be viewed without the benefit of hindsight afforded to the disclosure." *In re Paulsen*, 30 F.3d at 1482. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on Applicant' s disclosure. *See In re Vaeck*, 947 F.2d 488.

Accordingly, Applicants respectfully assert that the Manchitto Application and the Zimnyakov publication do not render independent claim 11 obvious. Thus, the 35 U.S.C. § 103(a) rejection of this claim is improper, and should be withdrawn.

C. **Rejections of Claims based on the Zimnyakov Publication**

It is respectfully asserted that the Zimnyakov publication fails to teach, suggest or disclose the subject matter recited in amended independent claims 1 and 39 of the above-referenced application, and the claims which depend there from. Reasons for such assertion are provided herein below

In order for a claim to be rejected as anticipated under 35 U.S.C. § 102(b), each and every element as set forth in the claim must be found, either expressly or inherently described, in a single prior art reference. Manual of Patent Examining Procedures, §2131; *also see Lindeman Machinenfabrik v. Am Hoist and Derrick*, 730 F.2d 1452, 1458 (Fed. Cir. 1984).

In order for a claim to be rejected for obviousness under 35 U.S.C. § 103, not only must the prior art teach or suggest each element of the claim, the prior art must also suggest combining the elements in the manner contemplated by the claim. *See Northern Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931, 934 (Fed. Cir.), *cert. denied* 111 S.Ct. 296 (1990); *see In re Bond*, 910 F.2d 831, 834 (Fed. Cir. 1990). "It is improper to use the inventor's disclosure as a road map for selecting and combining prior art disclosures." *See Grain Processing Corp. v. American Maize-Products Corp.*, 840 F.2d 902, 907 (Fed. Cir. 1988). "[T]he reference must be viewed without the benefit of hindsight afforded to the disclosure." *In re Paulsen*, 30 F.3d 1475, 1482

(Fed.Cir. 1994). The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on Applicant' s disclosure. *See In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

Applicants' invention, as recited in amended independent claim 1 (which includes the subject matter of now-cancelled claims 5 and 6), relates to a method of analyzing tissue, which comprises the steps of, *inter alia*:

> illuminating a tissue with coherent or partially coherent light;
>
> receiving light reflected from the tissue at a detector and forming series of speckle patterns; and
>
> **analyzing changes in the speckle patterns at time intervals sufficient to measure changes caused by microscopic motion of objects within the tissue, wherein the tissue is at least one of in vivo or an internal tissue.**

Applicants' invention, as recited in amended independent claim 39 (which includes the subject matter of now-cancelled claims 5 and 6), relates to a method of analyzing a tissue structure, which comprises the steps of, *inter alia*:

> illuminating the tissue structure with coherent or partially coherent light;
>
> receiving light reflected from the tissue structure at a detector and forming a series of speckle patterns;
>
> gathering speckle pattern data at time intervals sufficient to measure microscopic motion within the tissue structure or adjacent tissue; and
>
> **assessing the tissue structure by analyzing spatial characteristics of the speckle pattern data to deduce structural or biomechanical characteristics of the tissue structure, wherein the tissue structure is at least one of in vivo or an internal tissue structure.**

In the Office Action dated March 8, 2005, the Examiner never rejected claims 5 and 6 of the above-identified application as being anticipated by or obvious over the Zimnyakov publication. Thus, the Examiner effectively agreed that the Zimnyakov publication fails to teach,

suggest or disclose **analyzing changes in the speckle patterns at time intervals sufficient to measure changes caused by microscopic motion of objects within the tissue** ***(which is in vivo and/or an internal tissue)***, as recited in amended independent claim 1, or **assessing the tissue structure by analyzing spatial characteristics of the speckle pattern data to deduce structural or biomechanical characteristics of the tissue structure** ***(which is in vivo and/or an internal tissue)***, as recited in amended independent claim 1. This feature was included in now-cancelled claims 5 and 6 which previously depended on independent claim 1, and these claims were not rejected based on the Zimnyakov publication.

Indeed, Applicants agree with the Examiner that the Zimnyakov publication fails to teach, suggest or disclose that the analysis recited in amended independent claims 1 and 39 is performed on the tissues or tissue structures that are in vivo and/or internal tissues/tissue structures.

Therefore, Applicants respectfully submit that the Zimnyakov publication fails to teach, suggest or disclose the subject matter recited in amended independent claims 1 and 39. Thus, the 35 U.S.C. § 102(b) rejection of amended independent claims 1 and 39, and the §§ 102(b) and 103(a) rejections of the claims which depend there from should be withdrawn. In addition, it is believed that various claims which depend from amended independent claims 1 and 39 are also allowable over the Zimnyakov publication for at least the same reasons, as well as contain separately patentable subject matter.

III. ALLOWABLE SUBJECT MATTER

In the Office Action dated March 8, 2005, the Examiner confirmed that the previously-pending claims 26, 70 and 71 would be allowed if rewritten in independent form to include the recitations of the respective base claim and any intervening claim. Claim 26 has been rewritten above to include the recitations of previously-pending independent claim 1, and amended to clarify the invention claimed therein. In addition, claims 70 and 71 have been rewritten above to include the recitations of previously-pending independent claim 1, certain features of other claims from which these claims depend from. Accordingly, Applicants respectfully request the Examiner to confirm that independent claims 26, 70 and 71 are allowed in the next communication.

IV. NEW CLAIMS 82 AND 83

New independent claims 82 and 83 have been added above to recite additional features of Applicants' invention. Support for these new claims can be found in the specification, drawings and originally-filed claims of the application. Applicants respectfully assert that independent claims 82 and 83 are allowable over the references relied on by the Examiner in the Office Action dated March 8, 2005. A conformation of allowability of these claims is respectfully requested.

V. CONCLUSION

In light of the foregoing, Applicants respectfully submit that pending claims 1-4, 7-27, 39-43, 62-69 and 72-83 are in condition for allowance. Prompt consideration, reconsideration and allowance of the present application are therefore earnestly solicited.

Respectfully submitted,

Dated: July 7, 2005

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Vulnerable Plaque Characterization Using Temporal and Spatial Speckle Analysis

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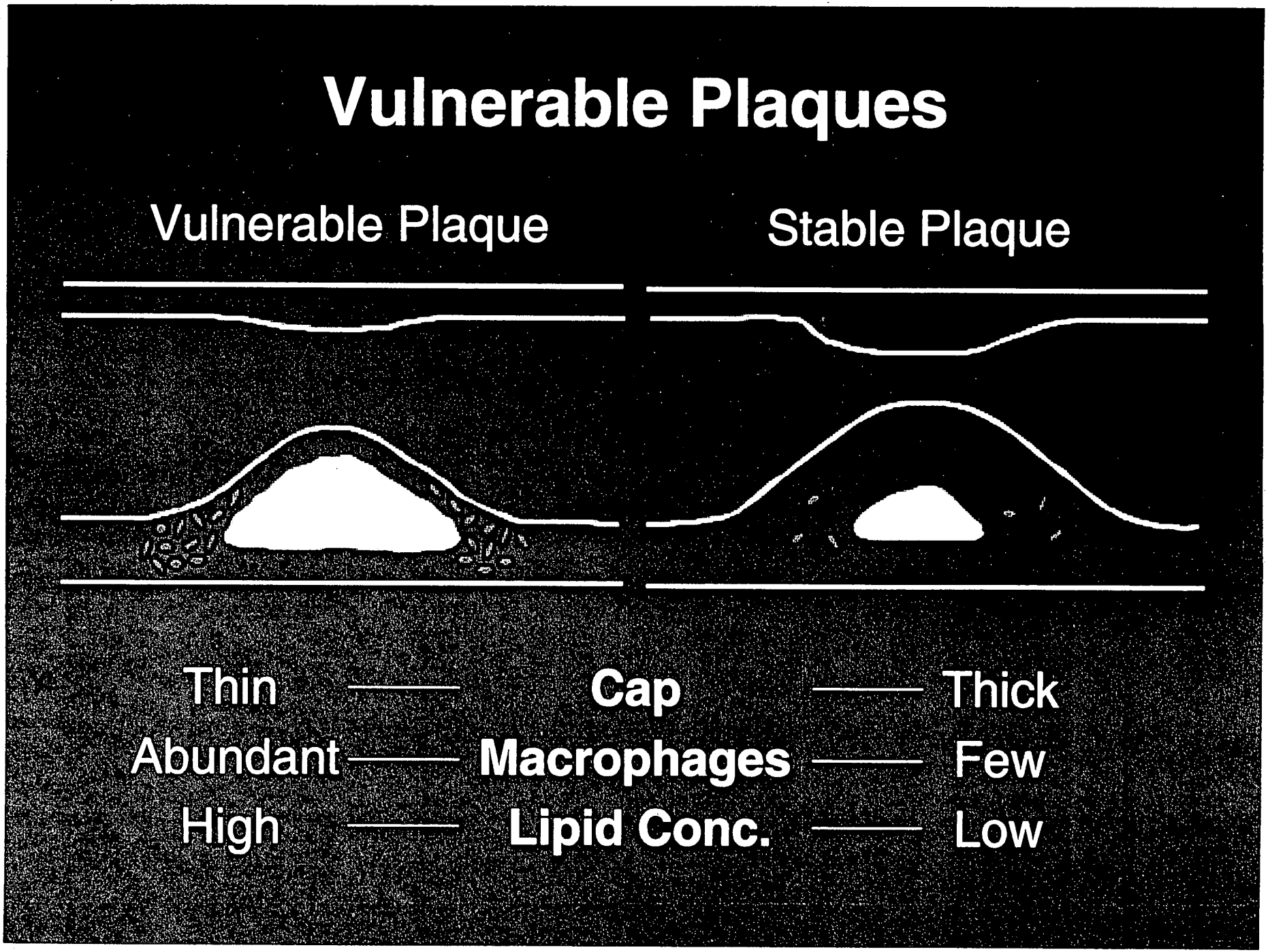
Vulnerable Plaques



Vulnerable Plaque Diagnosis

Proposed Diagnostics

- Infrared
  - Indirectly measures lipid content of plaque
- Fluorescence
  - Measures autofluorescence
    - Collagen
    - MMP
- IVUS
  - Structural measurement of cap
  - Poor resolution
- OCT
  - Structural measurement of cap
  - Sufficient resolution for measurement of cap thickness

Proposed methods do not measure the biomechanical properties of plaque

Intrinsic Plaque Biomechanics

Biomechanical properties

- Cap strength
  - **Proportional to thickness and structural integrity**
- Lipid pool
  - **Shear stress and strain on cap are related to lipid pool stiffness**
  - **Rupture of plaque tends to occur in areas of large stiffness gradient between cap and lipid pool**
  - **Lipid lowering drugs increase stiffness of lipid pool**
  - **Stiffening of the lipid pool decreases vulnerability**

Mechanical stiffness of the cap and lipid pool are essential parameters for assessing the likelihood of plaque rupture

Viscosity

Viscosity of tissue is proportional to stiffness

- Related to the ability of the molecules in the tissue matrix to move

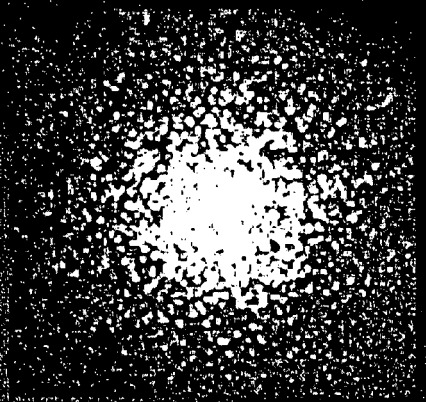
Brownian motion

- Random motion of particles in the matrix
- Brownian motion is inversely proportional to viscosity and stiffness
  - **Low stiffness, rapid Brownian motion**
  - **High stiffness, slow Brownian motion**

Brownian motion velocity is a measurement of tissue stiffness

Speckle

Coherent interference of light remitted from a scattering media or substrate



- Produces a grainy pattern at the surface of the specimen and in the image plane
- The pattern is created from the remitted field after many multiple scattering events within the specimen
- Motion of a single scatterer in the specimen changes the speckle pattern

Speckle Motion

Motion of a single scatterer in the specimen changes the speckle pattern

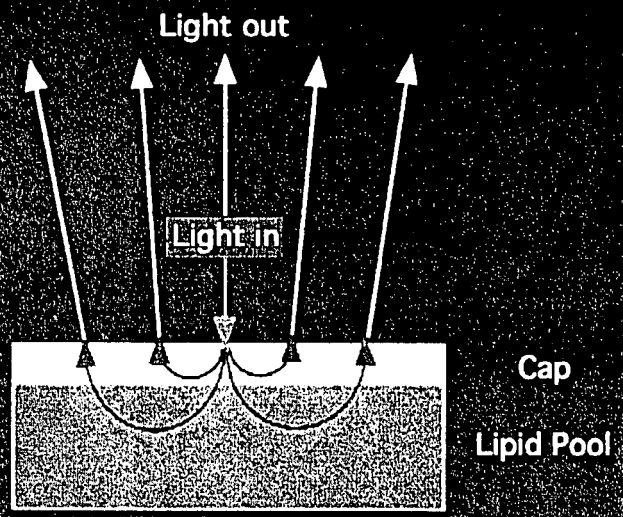
- The time dependent speckle pattern can be used to determine the Brownian motion within a multiply scattering media
- The motion is characterized by the spatial decorrelation of the speckle pattern as a function of time
- For Brownian motion, the decorrelation is a negative exponential with a time constant, τ

Stiffness of the cap and lipid pool can be determined by measuring the speckle decorrelation time constant

Light Diffusion

In tissue, light remitted further from the beam entry point has probed deeper into the tissue

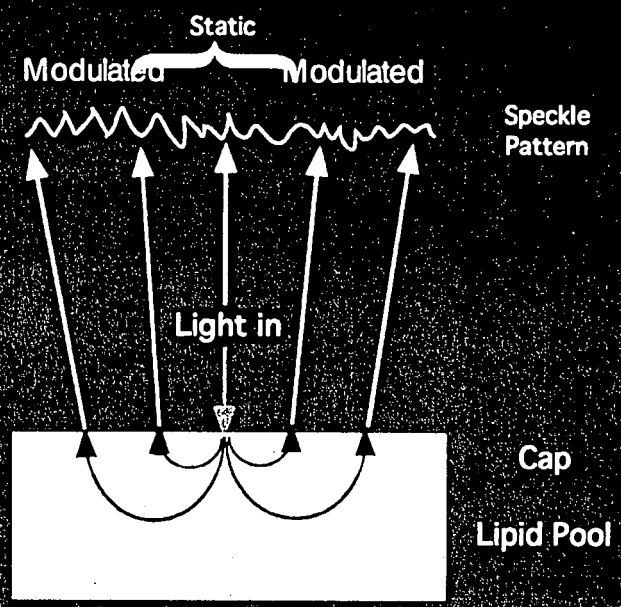
- Governed by the optical properties of tissue



Spatial and Temporal Characterization of Plaques

Measuring the speckle decorrelation time, τ, as a function of distance from beam entry point allows measurement of Brownian Motion and

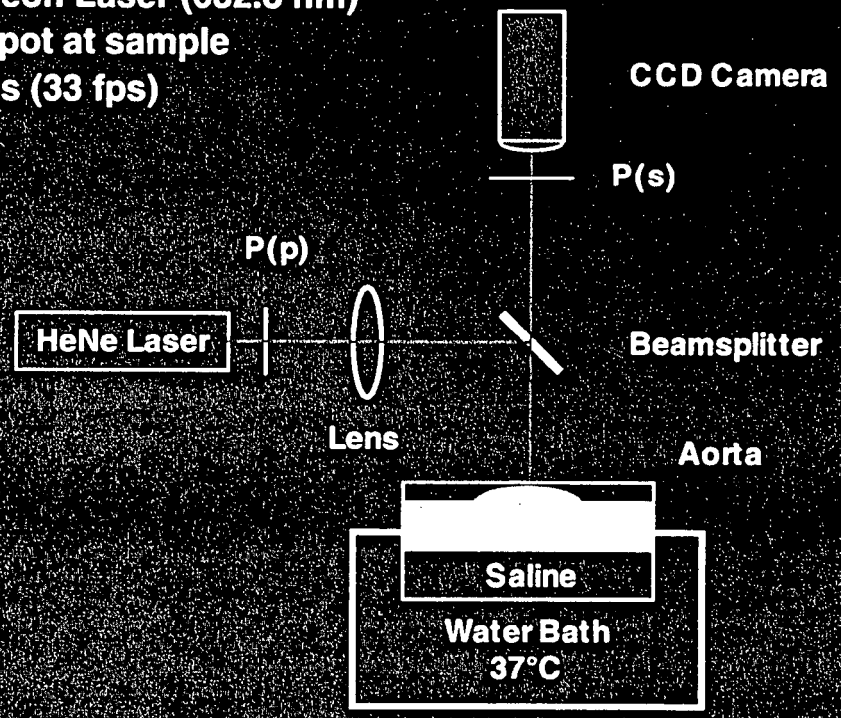
- Cap thickness
- Cap stiffness
- Lipid pool stiffness



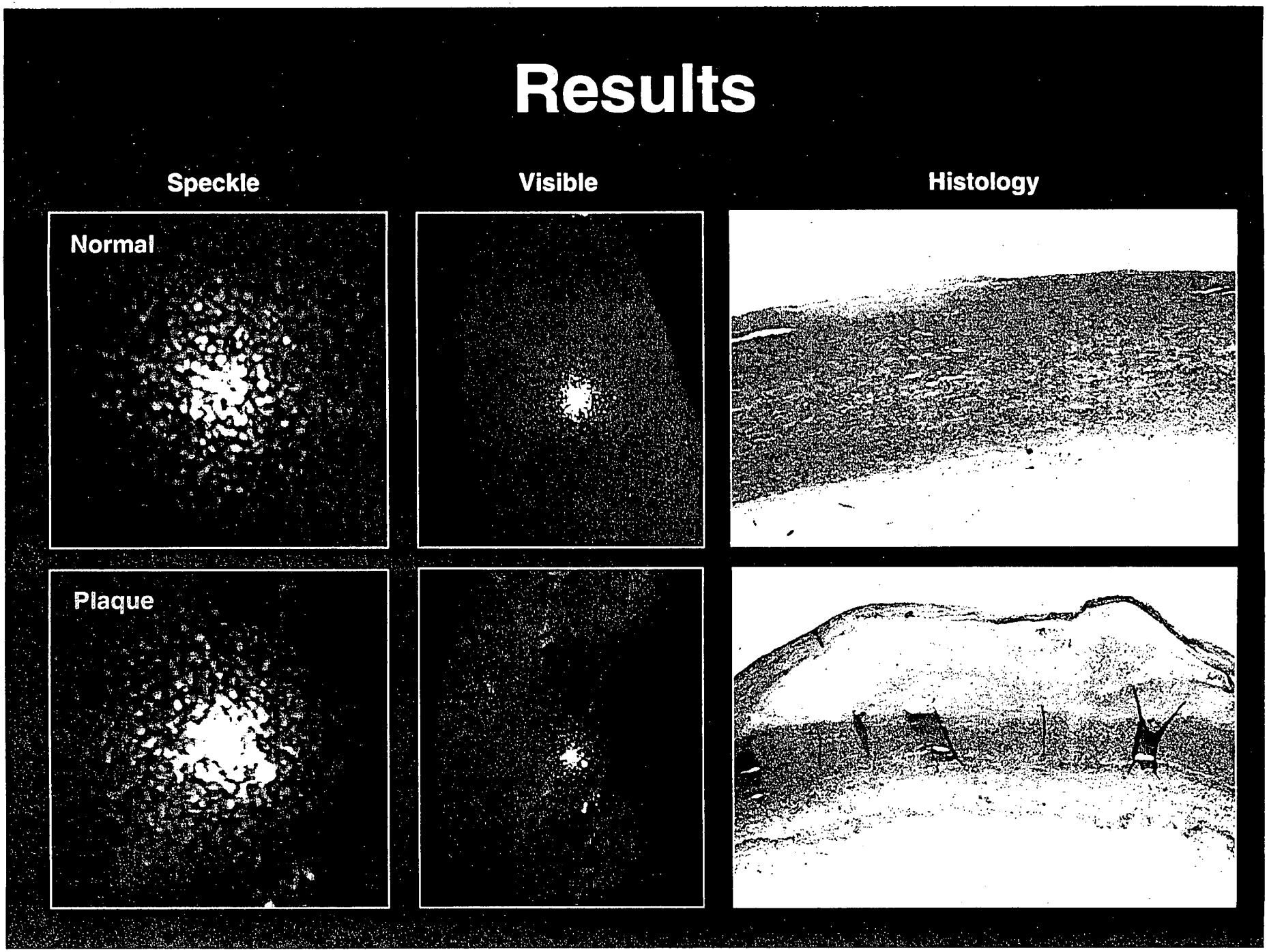
Proof of Principle

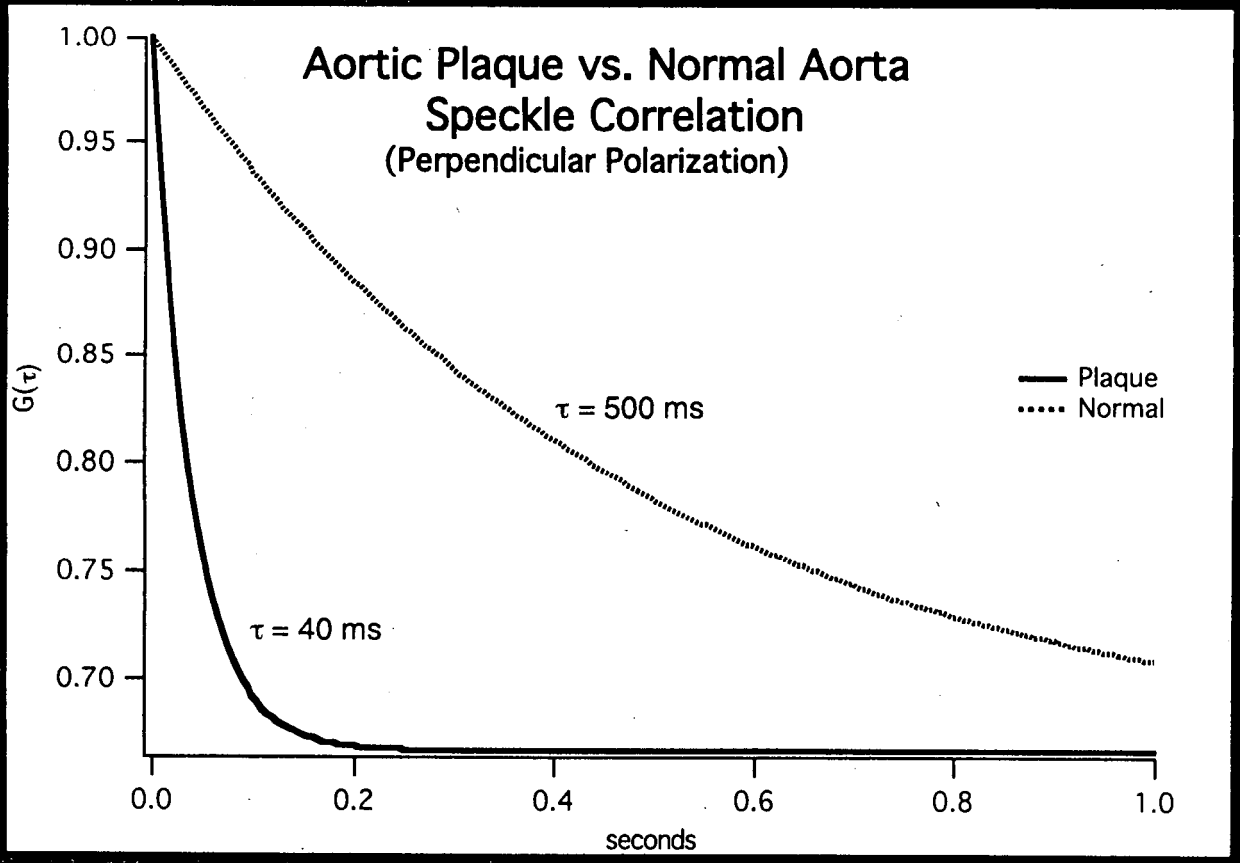
Methods

- Cadaveric aortas
- Normal saline, 37°C
- Helium Neon Laser (632.8 nm)
- 100 μm spot at sample
- 2 seconds (33 fps)



Results



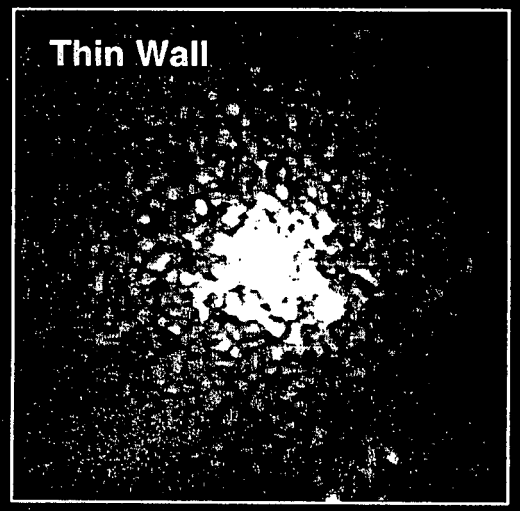


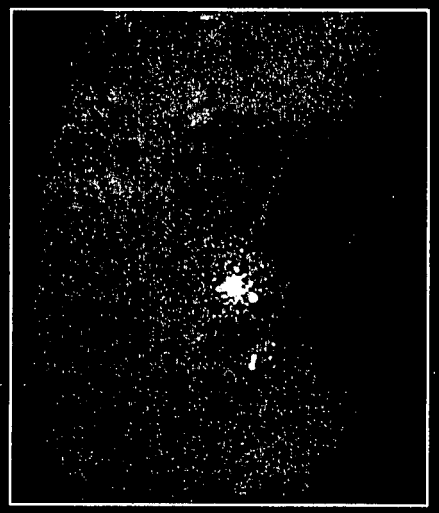
Speckle

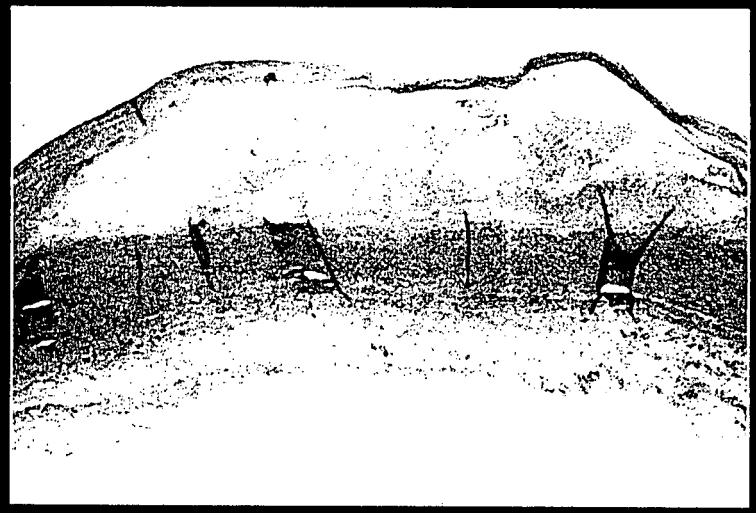
Visible

Histology

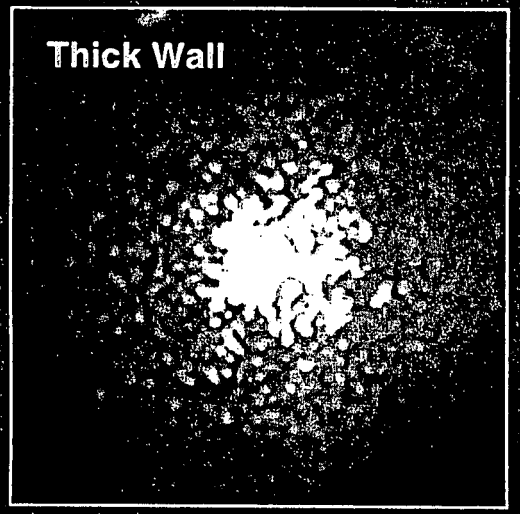
Thin Wall

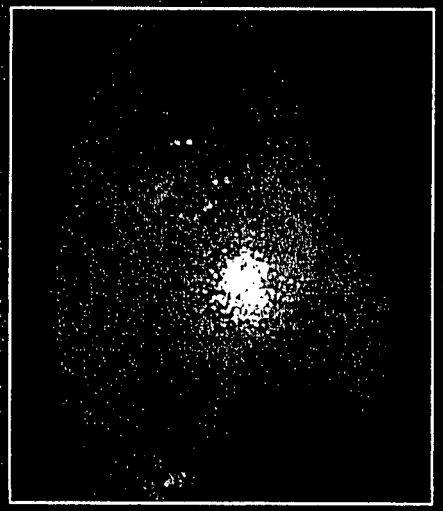


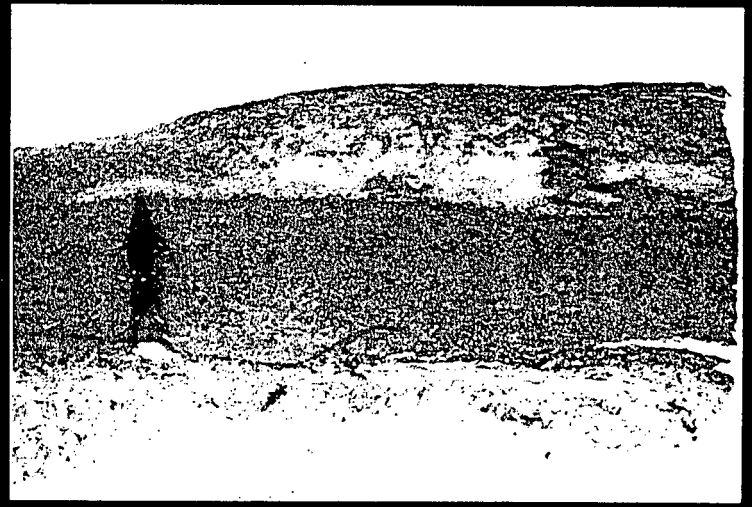


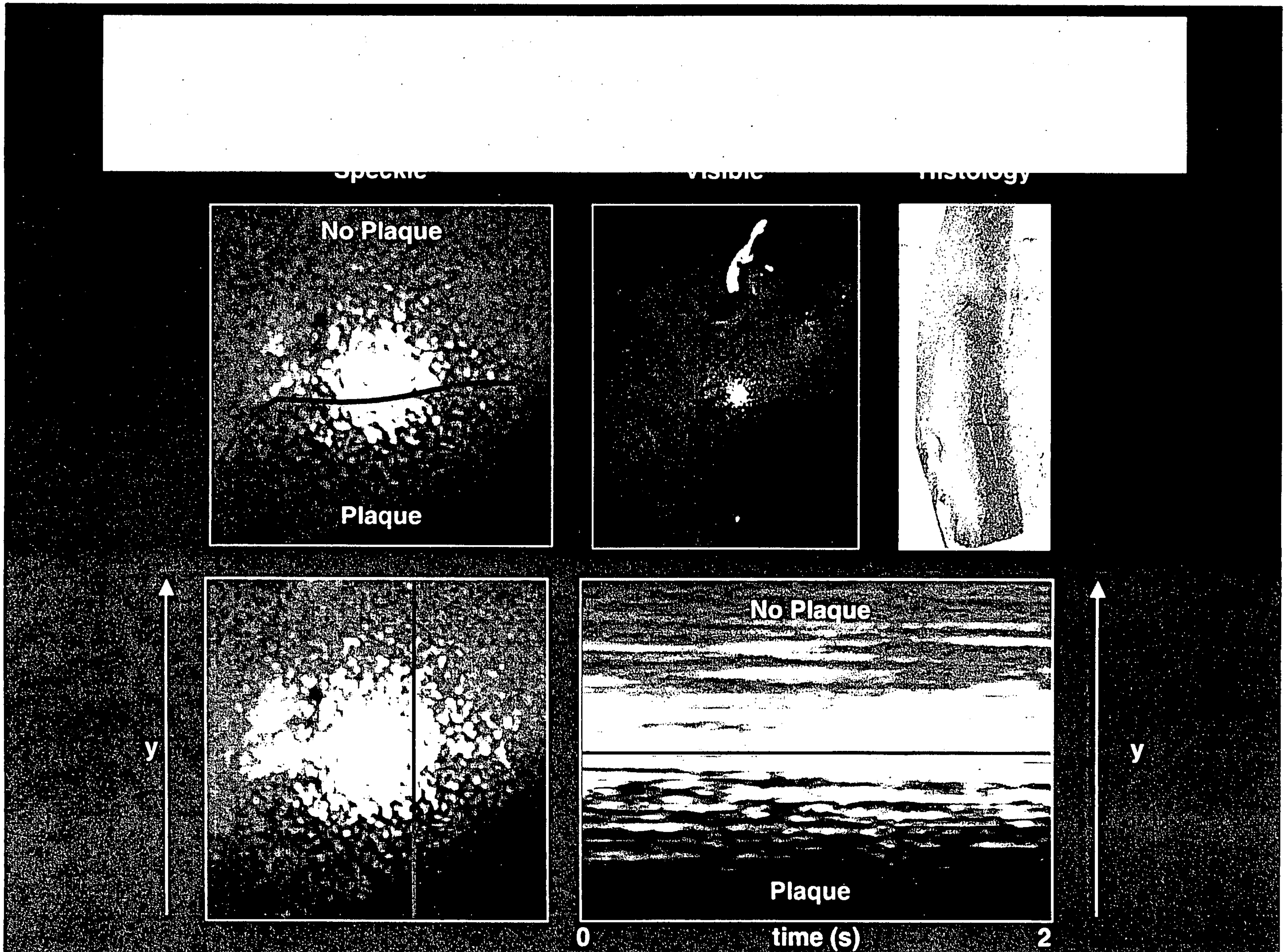


Thick Wall









Feasibility Study Summary

Speckle decorrelation time constant is different between normal aorta and plaque

- τ = 500 ms vs 40 ms

Speckle decorrelation time constant is different between thin and thick-walled plaques

- Greater for thick-walled plaques

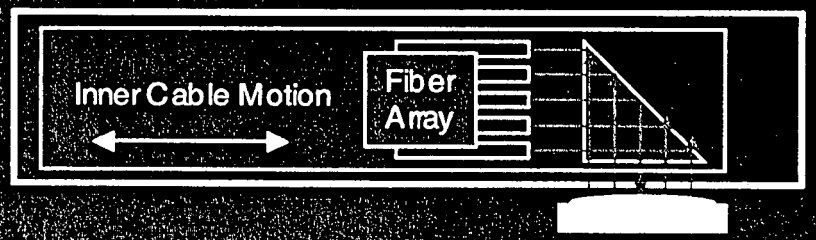
Speckle decorrelation is spatially dependent

- Border between plaque and normal aorta demarcates different speckle decorrelation time constants

Clinical Realization

Catheter based technique (one possibility)

- Array of fibers
- Scanned probe



Difficulties

- Intrinsic heart and catheter motion
  - **Lipid pool Brownian motion time constant is approximately 40 ms**
- Blood
  - **Will need saline infusion and/or direct contact with tissue**

Localize time and space (x, y, z) dependent speckle patterns using optical methods as opposed to light diffusion

- Confocal microscopy
  - Apertures in the source and detector planes combined with a high numerical aperture imaging lens
  - High resolution speckle analysis in (x, y, z)
  - Speckle decorrelation is less sensitive than multiple scattering technique
- Optical Coherence Tomography (OCT)
  - Uses low coherence interferometry to obtain localization in z
  - Measures cap thickness directly
  - Speckle decorrelation is less sensitive than multiple scattering technique

Conclusion

Temporal and spatial analysis of the speckle patterns can potentially determine

- Cap thickness
- Cap and plaque viscosity
- Spatially resolved biomechanical stiffness
- Plaque vulnerability

Future work

- Speckle statistics
  - **Can determine cap thickness and optical properties**
  - **Low coherence light**
- Strain and stress measurements
  - **Correlate biomechanical properties with Brownian motion measured by speckle decorrelation**
- Probe development
- Continue cadaveric aorta studies
- In vivo studies (e.g. rabbit model)

 JPF DYS

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APPLICATION NUMBER	FILING DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	DRAWINGS	TOT CLAIMS	IND CLAIMS
60/244,255	10/30/2000		75	00786-443P01/MGH - 1542	7		

FILING RECEIPT

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OC000000005675946

Date Mailed: 01/12/2001

Receipt is acknowledged of this provisional Patent Application. It will be considered in its order and you will be notified as to the results of the examination. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please write to the Office of Initial Patent Examination's Customer Service Center. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the PTO processes the reply to the Notice, the PTO will generate another Filing Receipt incorporating the requested corrections (if appropriate).**

Applicant(s)

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Brett E. Bouma, Quincy, MA ;

Continuing Data as Claimed by Applicant

Foreign Applications

If Required, Foreign Filing License Granted 01/12/2001

** SMALL ENTITY **

Title

Optical methods and systems for tissue analysis

Preliminary Class

Data entry by : DAVIS, SHERRY **Team :** OIPE **Date:** 01/12/2001

No Docketing Required
Reviewed by Practice Systems
Initials KYM On 1/19/01

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